



Pharmaceutical GMPs for the 21st Century

A Risk Based Approach/CBER Perspective

February 17, 2004

Mark A. Elengold

Deputy Director, Operations

Center For Biologics Evaluation and Research

Food and Drug Administration

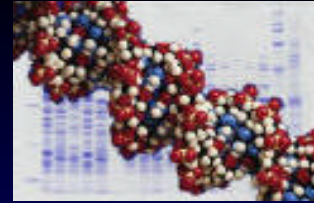
Commissioner's Strategic Plan

- **Science Based Risk Management**
- **Better informed consumers**
- **Patient Safety**
- **Counter-terrorism**
- **Strong FDA**
 - **Personnel, processes, infrastructure**
 - **Enhance availability of new technologies**

All highly pertinent to CBER and CBER products & CBER actions will support Plan.

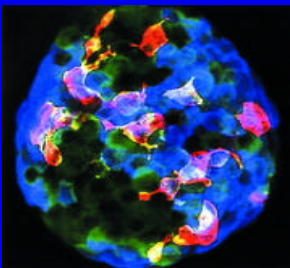


Vision for CBER



INNOVATIVE TECHNOLOGY ADVANCING PUBLIC HEALTH

- *Protect and improve public and individual health in the US and, where feasible, globally*
- *Facilitate the development, approval and access to safe and effective products and promising new technologies*
- *Strengthen CBER as a preeminent regulatory organization for biologics*



Vision: Protect and Improve Public and Individual Health

- *Safe & effective blood, vaccines and tissues*
 - Improved data and science based assessment methods, including employing multiple new technologies to improve efficiency and protect public health
 - Efficient and appropriate science based review
- *Product development/evaluation/preparedness for counter-terrorism and for emerging infectious diseases*
 - New approaches needed: e.g. Bioshield, platform technologies: while assuring safety, confidence
- *Risk based regulation*
 - Enhance risk based assessment & decision making to improve targeting and efficiency of regulatory process

CBER/CDER Consolidation

<u>PRODUCT</u>	<u>CBER</u>	<u>CDER</u>
IND	1748	1162
IDE	163	1
BLA (approved)	1259	59
BLA (pending)	36	9
NDA (approved)	60	3
NDA (pending)	1	0
PMA (approved)	18	0
PMA (pending)	3	0
510k (approved)	671	0
510k (pending)	26	0
ANDA (approved)	8	0



The Regulatory Pendulum

Centralization

Enforcement

Legal emphasis

Privatization

Process



Decentralization

Education

Science-based

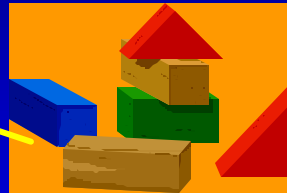
Government

Content

Earmarks of New Era



Risk



Systems



Advanced
Technology

Risk

- **Product**

- What can go wrong?
- What is the likelihood?
- What are the consequences?

- **Process**

- Identification of critical processes
- Identification of critical process points
- Control critical process points

- **Regulatory**



Risk Analysis Process

Use research and scientific information

in quantitative analyses to

inform risk management strategies

- Estimates likelihood & magnitude of risk
- Evaluate and compare interventions
- Define data gaps and research needs



Risk Assessment Applied to Drug Quality

- Control of process steps critical to product performance
- Focus on what is important
- Requires knowledge of physical and chemical attributes that affect product performance
- Life cycle
- Facilitated by technology (chemical and engineering)

Current Good Manufacturing Practice (cGMP)

- Application of quality assurance and control principles to drug manufacturing
- Required by Congress more than 40 years ago
- cGMP Regulations
 - 21 CFR Parts 210 and 211
 - Most issued 25 years ago



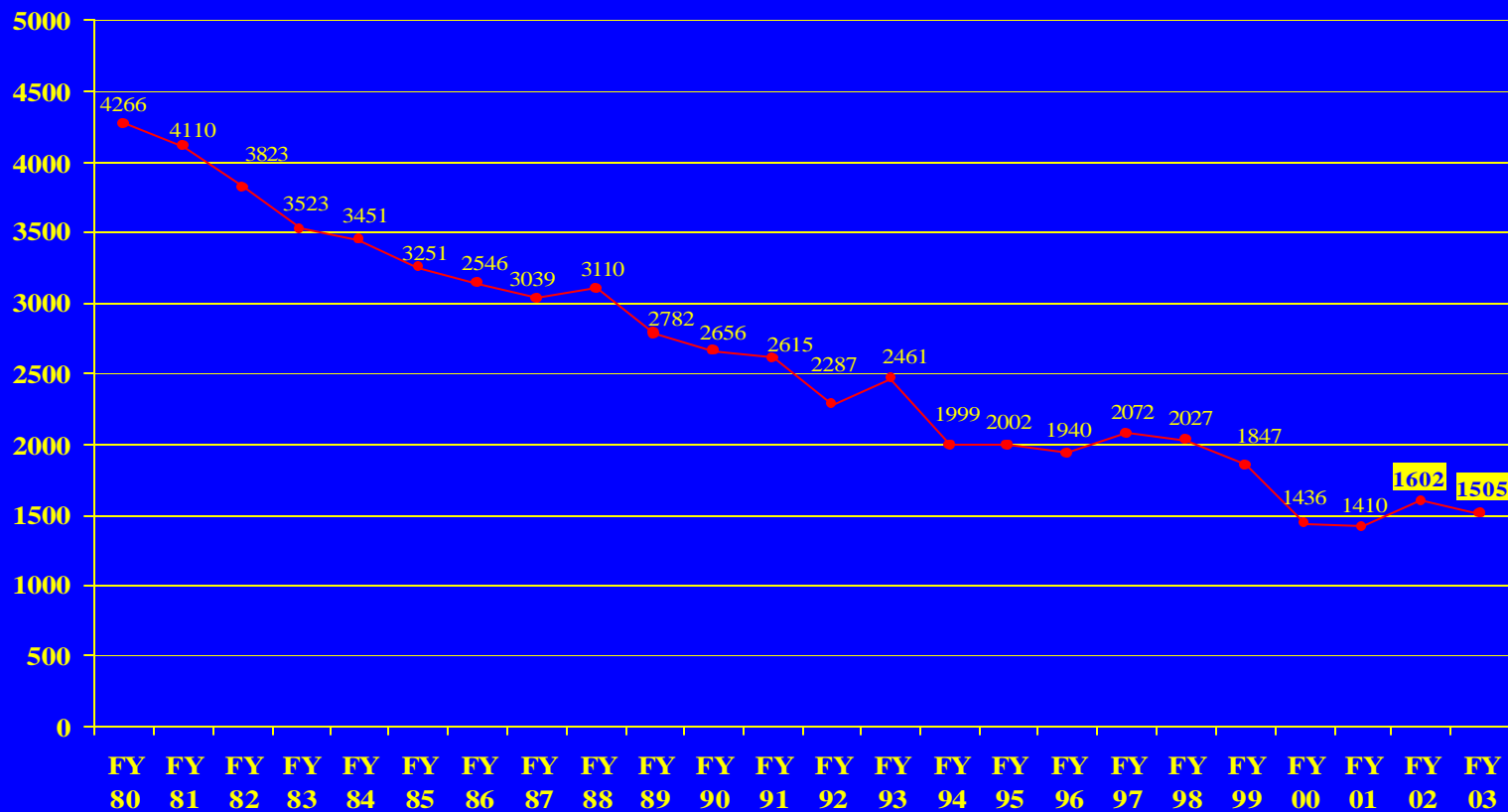
Assurance of cGMP Compliance

- **Pre-market application review**
 - Chemistry and manufacturing controls (CMC)
- **Inspection of manufacturing facilities**
 - Conformance to cGMP
 - Pre- and Post-market

Changes Driving the Evaluation

- Increase in the number of pharmaceutical products and the role of medicines in health care
- Decrease in frequency of biennial inspections as a result of fewer resources

Domestic cGMP Drug Inspections



Changes Driving the Evaluation

(continued)

- **Advances in the pharmaceutical sciences and manufacturing technologies**
- **The use of biotechnology in drug discovery and manufacturing**
- **Advances in the science of quality**
- **Globalization of the pharmaceutical industry**



Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach

- **Agency initiative announced on August 21, 2002**
- **Two-year + program**
- **Applies to pharmaceuticals, including biological human drugs and veterinary drugs (excludes blood/plasma)**



Objectives

- **Ensure regulatory review and inspection policies are based on state-of-the-art pharmaceutical science**
- **Encourage adoption of new technological advances by pharmaceutical industry**

Objectives

(continued)

- **Integrate advances in quality management techniques, including quality systems approaches, into Agency's regulatory standards and systems for review and inspection processes**
- **Implement risk-based approaches**
- **Enhance consistency and coordination of Agency drug quality programs**

Progress

- **Oversight**

- **Steering committee**

- CBER
 - CDER
 - CVM
 - ORA
 - Office of the Commissioner

- **Working groups**

- **Six-month and 1 year milestones completed**



Guidance

<http://www.fda.gov/cber/guidelines.htm>

- **Draft Guidance for Industry:
Comparability Protocols - Protein
Drug Products and Biological
Products - Chemistry, Manufacturing,
and Controls Information - 9/3/2003**
- **Guidance for Industry: Part 11,
Electronic Records; Electronic
Signatures — Scope and Application -
9/3/2003**



Guidance (continued)

<http://www.fda.gov/cber/guidelines.htm>

- **Draft Guidance for Industry: Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP - 9/3/2003**
- **Draft Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice - 9/3/2003**



21 CFR Part 11 Implementation

- Clarifies scope and application of regulation
- Provides enforcement discretion in certain problematic areas



Encourage Innovation Within Existing Framework

- **Draft Guidance for Industry on “Comparability Protocols – Chemistry, Manufacturing, and Controls Information”**
- **Applies to non-protein pharmaceuticals and veterinary drugs**
- **Facilitates continuous improvement and innovation**

Center Review of Drug cGMP Warning Letters

- All drug cGMP Warning Letters will be reviewed by the relevant Center prior to issuance
- Starts March 1, 2003
- Will help identify and resolve possible program inconsistencies before Warning Letter is issued



Technical Dispute Resolution Process for cGMP Disputes

- To allow for discussion of scientific and technical issues
- Bring the best technical expertise to bear on the particular issue
- Allow development of best practices and policies across FDA
- Improve transparency of the regulatory process



Form FDA 483

● Additional standard language:

- “This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.”



Scientific Workshops

- **“A Drug Quality System for the 21st Century”**
 - **April 22-24, 2003**
 - **Washington, DC**
 - **Topics**
 - Risk-based cGMP
 - Integrated systems approach to the CMC review and cGMP inspections
 - Post approval manufacturing changes
 - Manufacturing science
 - Summary - <http://www.fda.gov/cder/gmp/pqri-MfgSciWkshp.htm>



Risk-Based Approach to Work Planning Process

- **Prioritization based on higher-risk pharmaceutical manufacturing sites, e.g.,**
 - **Sterile drug manufacturers**
 - **Prescription drug manufacturers**
 - **New registrants not previously inspected by FDA**
 - **Medical gas manufacturers/repackers**

Improving Operations of Team Biologics

- **Adopt internal quality management system**
- **Develop metrics to determine impact on industry**
- **Standardize training and qualifications of Core Team members**
- **Risk-based work planning**
- **Increased communications between headquarters and field**

Product Specialists

- **Exploring possible approaches to include product and technical specialists on inspection teams**
 - **Product Specialists already participate on Team Biologics inspections**
- **Enhance technical quality and consistency of inspections**
- **Facilitate adoption of innovative manufacturing technologies**

Ongoing/Future Initiatives

- **International collaboration**
- **Pharmaceutical inspectorate**
- **Process Analytical Technologies (PAT) initiative**
- **Contract**

Keys to Success

- **Defining quality**
- **Risk assessment procedures**
- **Aligning CMC review and inspections**
- **Measuring outcomes**



U.S. Food and Drug Administration



CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

[FDA Home Page](#) | [CBER A-Z Index](#) | [CBER Site Map](#) | [Contact CBER](#)

[Blood](#) | [Therapeutics](#) | [Vaccines](#) | [Cellular/Gene Therapy](#) | [Allergens](#) | [Tissue](#) | [Devices](#)
[Products](#) | [Manufacturers](#) | [Healthcare](#) | [Reading Room](#) | [Meetings](#) | [About Us](#)

What's New at CBER

Product Approvals

- Botulism Immune Globulin Intravenous (Human), (BabyBIG)

Recalls

- Recall of Immune Globulin Intravenous (Human) 10% Solvent/Detergent Treated, Gamimmune

Guidances

Safety Information

Consumer Information

Transfer of Therapeutic Products to CBER

Countering Bioterrorism

Information available on Anthrax; FDA and CDC's Bioterrorism Information; FAQs

Vaccine Adverse Event Reporting System (VAERS)

Monkeypox Virus Infections and Blood & Plasma Donors

Smallpox

Severe Acute Respiratory Syndrome (SARS)

Postmarketing Study Commitments

CBER Research

Search

Powered by Google

CBER Index from A-Z

CBER Site Map

Jobs at CBER

Subscribe to CBER

Receive email notifications of all new guidances, recalls and talkpapers

Contact CBER

Impact of Severe Weather Conditions on Biological Products

Updated November 24, 2003

[CBER A-Z Index](#) | [CBER Site Map](#) | [Contact CBER](#)
[FDA Home Page](#) | [Search FDA Site](#) | [FDA A-Z Index](#) | [Contact FDA](#) | [Privacy](#) | [Accessibility](#) | [HHS Home Page](#)

[CBER A-Z Index](#) | [CBER Site Map](#) | [Contact CBER](#)
[FDA Home Page](#) | [Search FDA Site](#) | [FDA A-Z Index](#) | [Contact FDA](#) | [Privacy](#) | [Accessibility](#) | [HHS Home Page](#)

FDA/ Center for Biologics Evaluation and Research



We're Here to Help You!

WWW.FDA.GOV/CBER

- **Email CBER:**

- **Manufacturers:**

- matt@cber.fda.gov**

- **Consumers, health care professionals:**

- octma@cber.fda.gov**

- **Phone:**

- **01-301-827-1800**

